



Management strategies of Barrett's esophagus

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Abstract

Barrett's esophagus is a condition resulting from chronic gastro-esophageal reflux disease with a documented risk of esophageal adenocarcinoma. Current strategies for improved survival in patients with Barrett's adenocarcinoma focus on detection of dysplasia. This can be obtained by screening programs in high-risk cohorts of patients and/or endoscopic biopsy surveillance of patients with known Barrett's esophagus (BE). Several therapies have been developed in attempts to reverse BE and reduce cancer risk. Aggressive medical management of acid reflux, lifestyle modifications, antireflux surgery, and endoscopic treatments have been recommended for many patients with BE. Whether these interventions are cost-effective or reduce mortality from esophageal cancer remains controversial. Current treatment requires combinations of endoscopic mucosal resection techniques to eliminate visible lesions followed by ablation of residual metaplastic tissue. Esophagectomy is currently indicated in multifocal high-grade neoplasia or mucosal Barrett's carcinoma which cannot be managed by endoscopic approach.

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Key words: Barrett's esophagus; Diagnosis; Manage-

INTRODUCTION

Barrett's esophagus (BE) is a condition resulting from chronic gastro-esophageal reflux disease (GERD). The clinical importance of the definition of BE is that it should identify a lesion documented to be at risk of esophageal adenocarcinoma.

Presently, the diagnosis of BE is based on a combination of endoscopic and histologic criteria^[1,2]. The diagnosis of BE is established when intestinal metaplasia (IM) is found in biopsy specimens obtained from salmon-colored mucosa in the distal esophagus proximal to the gastro-esophageal junction (Figure 1).

DIAGNOSIS

The diagnosis of BE requires systematic biopsy of the abnormal-appearing esophageal mucosa to document IM and to detect dysplasia^[1]. The "Seattle" protocol with random four-quadrant biopsies taken at 1-2-cm intervals along the endoscopically visible BE is the current recommended procedure in guidelines for the detection of dysplasia in patients with established BE^[3-6].

BE is currently graded with use of the Prague circumference and maximum criteria, which is a standardized, validated system based on the circumferential and

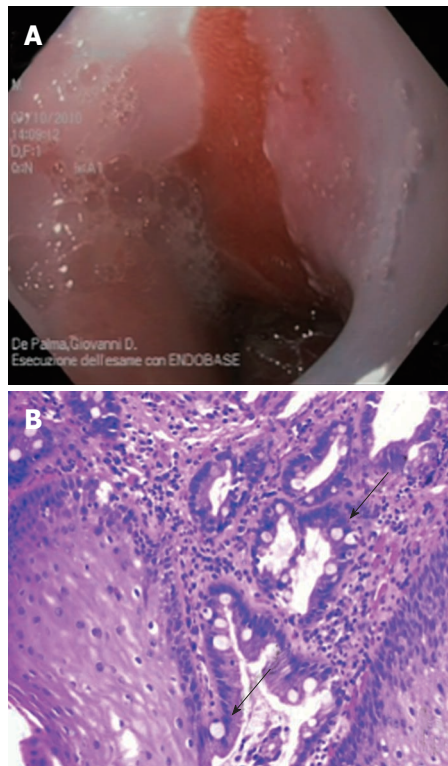


Figure 1 Endoscopic and histologic images of Barrett's esophagus. A: Endoscopic view of salmon-colored mucosa above the gastro-esophageal junction; B: Intestinal metaplasia with goblet cells (arrows) was found in biopsy specimens at histology.

maximal extent of the columnar-lined esophagus^[7-9].

THE PROBLEM: WHY, WHO, WHEN AND HOW TO TREAT FOR BE

BE develops in approximately 5% to 15% of patients with gastro-esophageal reflux undergoing endoscopic evaluation and in 1% to 2% of unselected population undergoing endoscopy^[10-14]. Evidence from one case series suggests that at least 60% of patients with BE develop the disease as a result of chronic reflux; other condition of mucosal inflammation of the lower esophagus, such as mucosal damage by chemotherapy, non-steroidal anti-inflammatory drugs, and viral infections are associated with the development of BE in about 1% of cases respectively^[15-19].

BE is associated with an increased risk of adenocarcinoma of the esophagus. Patients with BE are about 40 times more likely to have esophageal adenocarcinoma (EAC) than those without IM. The risk for an individual patient with BE has been estimated to range from 1 in 50 to 1 in 200 patient-years, or roughly 0.5% per year. Recent large cohort studies suggest the rate of progression is 0.1%-0.3% per year^[20-23].

Barrett's adenocarcinoma is considered a multistep process evolving from normal squamous mucosa to metaplasia to dysplasia to carcinoma. Why such a progression occurs, who is at risk, and what promotes these

changes remain unclear. Clinical and demographic factors, such as, age, male gender, longer duration and increased frequency of GERD symptoms, length of BE segment are associated with modestly increased odds of progression to EAC in some studies^[24-29]. Biomarkers^[30-33] such as aneuploidy and p53 loss have been recently associated with increased risk of progression to high-grade dysplasia (HGD) and/or EAC^[34-37].

At present, the strongest known predictor of cancer risk in the setting of BE is the degree of dysplasia. Subjects with no dysplasia have extremely low cancer rates for the five years following the index endoscopy. Conversely, subjects with HGD have rates reported as high as 10% per year^[38-40].

It is of paramount importance that the correct diagnosis is established. In many instances, especially in the presence of severe inflammation, there is an inter-observer disagreement on the diagnosis and grading of dysplasia. All biopsies with suspected dysplasia should be reviewed by a second "expert" pathologist^[41-43].

Several therapies have been developed in attempts to reverse BE and reduce cancer risk. Aggressive medical management of acid reflux, lifestyle modifications, anti-reflux surgery^[44-49], and endoscopic treatments^[50-52] have been recommended for many patients with BE. Whether these interventions are cost-effective or reduce mortality from esophageal cancer remains controversial.

MANAGEMENT STRATEGIES

Screening and surveillance for BE

Current strategies for improved survival in patients with Barrett's adenocarcinoma focus on detection of dysplasia. This can be obtained by screening programs in high-risk cohorts of patients and/or endoscopic biopsy surveillance of patients with known BE.

There is inadequate evidence of benefit to recommend endoscopic screening for BE in the general population of patients with GERD who do not have risk factors^[53-58]. Well-established risk factors for BE include age older than 50 years, male sex, white race, chronic GERD^[1-5], hiatal hernia^[59], elevated body mass index, and intra-abdominal distribution of body fat^[60,61]. The risk factors can be used to determine the threshold for endoscopy in patients with GERD to screen for the presence of BE^[2].

Endoscopic surveillance for patients with BE is recommended to identify curable neoplasia. Survey data indicate that although surveillance is widely practiced, there is marked variability in the technique and interval of surveillance because practice guidelines are not widely followed (Table 1)^[62].

Endoscopic imaging for the detection of dysplasia and early cancer: Endoscopy with multiple systematic biopsies (the "Seattle" protocol) is needed for the detection of dysplasia or adenocarcinoma for the surveillance of BE. This approach, requiring a large number of

Table 1 Guidelines for evaluation and management of Barrett's esophagus

	ACG	ASGE	AGA	BSG
No-dysplasia	Two esophageal examination with biopsy within 1 yr and follow up with endoscopy every 3 yr	Two consecutive esophageal examination with biopsy within 1 yr and follow up with endoscopy every 3 yr	Assess within 1 yr and if no dysplasia, defer for 5 yr or until cancer therapy is not possible of life expectancy is limited	Surveillance every 2 yr, if appropriate
Indefinite -	-	Repeat biopsy after 8 wk of acid suppression, if evidence of acute inflammation due to gastro-esophageal acid reflux	-	Assess with extensive biopsies after course of proton pump inhibitors and return to routine surveillance, if no definite dysplasia at 6 mo
LGD	Treat based on highest grade of dysplasia seen on two esophageal examinations within 6 mo, with pathologist's confirmation, and follow up with endoscopy every year until dysplasia is absent on two subsequent examinations	Follow up after 6 mo with concentrated biopsies in area of dysplasia; follow up every 12 mo if dysplasia persists	Assess in 1 yr and re-examine every year if dysplasia is confirmed by two pathologists (if there is disagreement about the presence of dysplasia then re-examine in 2 yr)	Extensive biopsy after intensive acid suppression for 8-12 wk; surveillance every 6 mo if dysplasia persists; surveillance intervals of 2-3 yr if regression occurs on two sequential examinations
HGD	Document any mucosal irregularities, repeat esophageal examination with biopsy within 3 mo, with pathologist's confirmation, to eliminate the possibility of cancer; follow up with endoscopic mucosal resection in the case of any mucosal irregularity; then intensive endoscopic surveillance every 3 mo or an intervention, such as esophagectomy or ablation, in the case of flat mucosa	Diagnosis should be confirmed by a pathologist; surgical candidates can choose to have a surgery or endoscopic therapy; follow up patients who choose surveillance every 3 mo for 1 yr with several large biopsies every 1 cm along esophagus; after 1 yr without cancer detection, surveillance duration can be lengthened, provided dysplastic changes are absent on two subsequent examinations	Diagnosis should be confirmed by two pathologists; patients should be treated with surgical resection or endoscopic therapy; surveillance can be offered provided follow up with endoscopy is every 3 mo with a minimum of eight biopsies every 2 cm along esophagus	Esophagectomy recommended if changes persist after intensive acid suppression, if confirmed by two pathologists, and if patient considered fit for surgery; if unfit for surgery, use endoscopic ablation or mucosal resection

ACG: American College of Gastroenterology; ASGE: American Society for Gastrointestinal Endoscopy; AGA: American Gastroenterological Association; BSG: British Society of Gastroenterology; LGD: Low-grade dysplasia; HGD: High-grade dysplasia.

biopsies, is time consuming and has several limitations, including sampling error and inconsistent histological interpretation^[2-6].

Several endoscopic imaging techniques to improve the accuracy of endoscopic diagnosis, have been developed and tested recently, with variable results^[63-67]. Enhanced optical imaging techniques may improve the efficiency and accuracy of endoscopic surveillance^[68-72]. Enhanced techniques can generally be categorized as broad-field (red-flag) techniques, such as high-definition/high-resolution white-light endoscopy (HD-WLE) and narrow-band imaging (NBI)^[73-75], and focal techniques, such as confocal laser endomicroscopy (CLE)^[76-80]. The broad-field techniques are good for providing an overview of the entire BE segment, and point out an area of interest, whereas focal techniques can provide greater detail of the area of interest (Figures 2 and 3)^[81-85].

Recent reports demonstrated that, in BE patients undergoing surveillance endoscopy, CLE imaging with targeted biopsies significantly improved the yield of biopsies for dysplasia compared with standard endoscopy with random biopsies when CLE imaging is conducted on suspect areas evidenced with both HD-WLE and NBI. Similarly, CLE was useful as a tool to identify non-dysplastic BE, and hence potentially to reduce the number of biopsies needed^[86-89].

DRUG THERAPY

Acid suppressive therapy, specifically proton pump inhibitors (PPIs), has been shown to improve symptoms and to heal and prevent relapse of erosive esophagitis in patients with BE^[4,90,91]. Evidence to support use of PPIs, in patients with BE solely to reduce risk of progression to dysplasia or cancer is indirect and has not been proven in a long-term controlled trial^[92-96]. Epidemiologic data suggest a lower risk of progression in PPI users. There is also some evidence to suggest that long-term therapy may induce regression of IM and promote the development of squamous islands^[97-99].

There is epidemiologic and experimental evidence to suggest that chemoprevention using non-steroidal anti-inflammatory drugs, aspirin^[100-104], and selective cyclooxygenase-2 inhibitors^[105-107] may reduce the risk of cancer in BE patients. However, human trials to date has not proved that these treatments are associated with a lower risk for neoplastic progression^[108].

The A phase III, randomised study of aspirin and esoprazole chemoprevention in Barrett's metaplasia trial currently underway is seeking to determine the effects of high- and low-dose proton pump inhibitor therapy with and without low-dose aspirin as BE chemoprevention^[109,110].

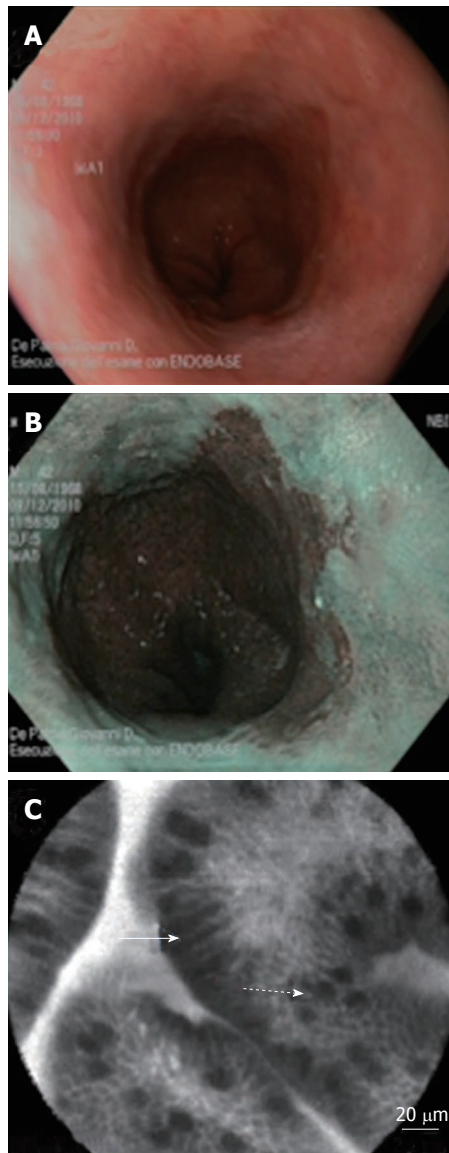


Figure 2 White-light and enhanced endoscopic images of non-dysplastic Barrett's esophagus. A: White-light of Barrett's esophagus; B: Narrow-band imaging endoscopic of Barrett's esophagus; C: Probe-based confocal laser endomicroscopy (pCLE) images of Barrett's esophagus. p-CLE image shows uniform villiform architecture, columnar cells (solid arrow) and dark goblet cells (dash arrow) predictive of non-dysplastic Barrett's esophagus.

ENDOSCOPIC THERAPY

Endoscopic treatment is focused on destruction of the existing metaplastic-dysplastic tissue using different modalities that eliminate the mucosa. The theory behind endoscopic treatment is that the injury of the metaplastic-dysplastic BE combined with vigorous acid suppression or with antireflux surgery would lead to reversion of the BE to squamous epithelium and reduce the risk of progression to cancer^[111-115].

Endoscopic treatment modalities include endoscopic resection techniques such as endoscopic mucosal resection and endoscopic submucosal dissection^[114] and endoscopic ablation therapy^[116,117], such as argon plasma coagulation (APC)^[118,119], laser ablation, photodynamic

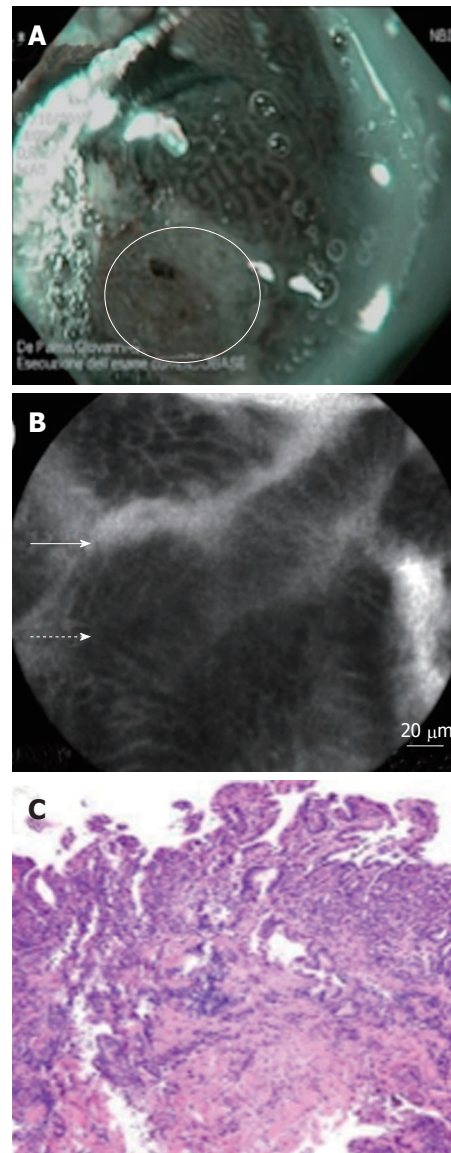


Figure 3 Enhanced narrow-band imaging and probe-based confocal laser endomicroscopy images of dysplastic Barrett's esophagus. A: Narrow-band imaging images shows distorted pits with irregular microvasculature (white circle); B: The corresponding probe-based confocal laser endomicroscopy image shows disorganized, distorted villiform structure and crypts, dark columnar cells (dash arrow) and dilated irregular vessels (solid arrow); C: High-grade dysplasia was found at histology in biopsy specimens performed at this level.

therapy (PDT)^[120], radiofrequency ablation (RFA)^[121,122], and cryotherapy^[123-127].

Current treatment requires combinations of mucosal resection techniques to eliminate visible lesions followed by ablation of residual metaplastic tissue. Endoscopic resection of focal lesions is currently the only method to accurately and reliably determine the depth of invasion of a superficial lesion since it is the only endoscopic technique that provides histology.

Several studies have reported on a variety of ablation methods and have demonstrated difficulty in achieving complete eradication of BE. Thermal ablative modalities, such as APC, and laser therapy suffer from several pitfalls including a not homogeneous ablation of the

mucosa and inconsistent depth of tissue penetration causing that some glands can persist under the neosquamous epithelium^[128,129].

At present, after the areas of mucosal abnormality are removed, ablation of the residual Barrett's mucosa is most commonly performed with PDT or RFA. Photodynamic therapy has been proved to be effective for dysplasia, with a success rate of > 90%. However, following this treatment, there is a high rate of complication and side effects, mainly characterized by strictures and photosensitivity^[12,120,130-132]. Radiofrequency ablation is associated with fewer complications since it has a limited depth of injury, although stricture formation is approximately 6% in some prospective series^[133-137]. After RFA, complete eradication of dysplasia was reported in > 90% of patients with LGD and > 80% of patients with HGD, 1 year after the initial treatment. After 3 years, complete eradication of dysplasia and complete eradication of IM was reported in 98% and 91% of patients, respectively. At 5 years follow up, complete eradication of IM was demonstrated in 92% of the patients^[138-142].

Buried metaplasia is reported less frequently after RFA (< 1%) than after other different ablative endoscopic therapies, including PDT. However RFA is a relatively new procedure and, therefore, available studies on RFA describe only brief follow-up intervals^[143,144].

Because of the esophagus remains after endoscopic therapy, surveillance endoscopy at regular intervals, is necessary, even after complete ablation of BE has been accomplished.

SURGICAL THERAPY

As development of BE is based on gastro-esophageal reflux, a potential concept would be to stop reflux by anti-reflux surgery and thereby interrupt the mechanisms of malignant degeneration. Patients who are appropriate surgical candidates may elect anti-reflux surgery^[145-148]. Fundoplication effectively controls reflux symptoms in most patients^[149,150]. Surgical control of reflux disease, however, has not been found to be associated with a decrease in the incidence of esophageal cancer^[151-154].

Before the advent of endoscopic therapies, esophagectomy was the primary treatment option for patients with HGD.

Esophagectomy offers the most definite treatment in patients with BE with HGD (in particular in patients with multifocal HGD) since it eliminates all of the Barrett's epithelium preventing the risk of progression. In patients with HGD, a benefit of esophagectomy includes the treatment of an occult carcinoma (surgical series summarizing the incidence of occult adenocarcinoma, in patients with the preoperative diagnosis of HGD in resected series show an incidence ranging from 0% to 73%)^[155-159].

The standard surgical resection in most patients includes a total esophagectomy with a transhiatal or trans-thoracic approach, and reconstruction with gastric pull-

up or tubularized gastric conduit and the anastomosis performed in the neck or the high chest. In some cases esophageal resection could be performed minimally invasively. Limited vagal-sparing surgery like esophageal stripping or Merendino's operation is currently indicated in multifocal high-grade neoplasia or mucosal Barrett's carcinoma which cannot be managed by endoscopic approach. Strong consideration should be given for the performance of surgery in a high-volume hospital, by a specialty-trained surgeon with a large-volume esophageal practice^[160-162].

CONCLUSION

BE is a premalignant condition, with dysplasia usually preceding the development of adenocarcinoma. Patients with chronic reflux, especially white males, have the highest risk. Reducing reflux either medically or surgically may diminish the occurrence and/or progression of disease. Management of BE may vary from essentially a surveillance strategy to highly invasive esophagectomy.

Several therapies have been developed in attempts to reverse BE and reduce cancer risk, such as medical management of acid reflux, antireflux surgery, and endoscopic treatments. Whether these interventions are cost-effective or reduce mortality from esophageal cancer remains controversial. Endoscopic mucosal ablation techniques show promise as emerging therapeutic options. Current treatment requires combinations of endoscopic mucosal resection techniques to eliminate visible lesions followed by ablation of residual metaplastic tissue.

Esophagectomy is currently indicated in multifocal high-grade neoplasia or mucosal Barrett's carcinoma which cannot be managed by endoscopic approach.

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